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Aldehyde-Selective Wacker Oxidation in a Thiyl-Mediated Vinyl Group Transfer Route to Daunosamine

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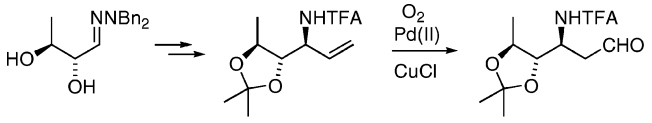
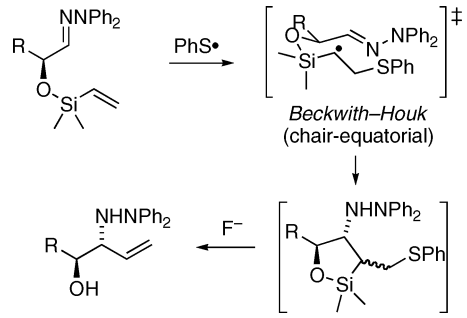
ABSTRACT



Asymmetric dihydroxylation, thiyl radical mediated transfer of a silicon-tethered vinyl group to a hydrazone and an unconventional aldehyde-selective Wacker oxidation are sequenced for an efficient synthesis of methyl *N*-trifluoroacetyl-L-daunosaminide in 32% overall yield from crotonaldehyde.

Asymmetric carbon−carbon bond constructions leading to chiral α-branched amines continue to offer challenges to the development of efficient methodology.[1] Among these methods, radical additions to imino compounds are endowed with certain advantages in chemoselectivity which make them attractive complements to polar methods.[2] However, methods for intermolecular addition of carbon-centered radicals are generally limited to alkyl radicals and do not accommodate intermolecular addition of a vinyl group. This goal has considerable synthetic potential due to the wide range of functional group transformations enabled by alkene functionality. We have developed such a vinyl addition in an indirect manner (Scheme 1), using a temporary silyl ether linkage between the radical precursor and acceptor groups to circumvent the intermolecular process.[3] In these reactions, thiyl radicals add to the vinyl group, generating an intermediate alkyl radical which undergoes 5-exo cyclization with the C═N bond of the hydrazone functionality. Treatment with fluoride then cleaves the temporary tether and causes elimination of benzenethiolate to regenerate the vinyl group of an allylic amino alcohol. The favored anti relative configuration is consistent with a chairlike Beckwith−Houk transition state[4] with the exocyclic substituent R equatorial. Thus, a tin-free diastereoselective radical addition of a vinyl group with "formal acyclic stereocontrol" may be realized under mild conditions using the silicon tether approach.[5]

Scheme 1



The presence of additional hydroxyl groups proved to be of little consequence to the excellent diastereocontrol (eq

(1) Reviews: (a) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315−1392. (b) Friestad, G. K. *Eur. J. Org. Chem.* **2005**, 3157−3172. (c) Zhou, P.; Chen, B.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003−8030. (d) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253−2329. (e) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995. (f) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. (g) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438.

(2) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461−5496.

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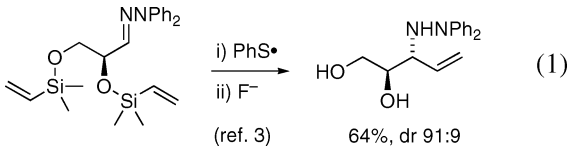
1),[3] and therefore this method was envisioned to be a potentially useful route for generation of polyhydroxylated amines such as aminosugars.[6] Oxidation of the vinyl group



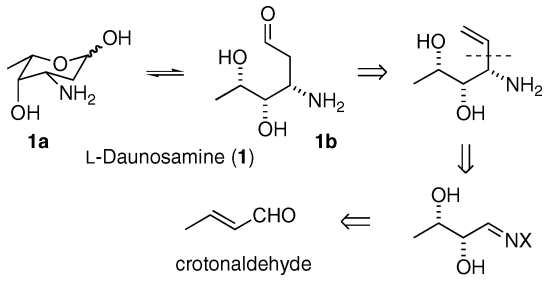
(1)

would be required to reach such targets, thereby offering an opportunity to broaden the scope of projected applications of the radical addition. Here we report the realization of these goals in a concise and efficient asymmetric synthesis of a 2,3-dideoxy-3-aminosugar from achiral precursors, using an unusual aldehyde-selective Wacker oxidation as a key step.

Aminosugars such as daunosamine are found within oligosaccharides, glycopeptides, and anthracycline antitumor antibiotics; their importance as synthetic targets stems from not only their presence within natural products but also their interesting applications in bioorganic and medicinal chemistry.[7,8] Typically, these building blocks are prepared in lengthy sequences from carbohydrates, a strategy which is inherently limited to those sugar starting materials which are readily available. We hoped to demonstrate a novel combination of the Si-tethered radical addition method with asymmetric catalysis to access L-daunosamine (**1**)[9] as a prototypical member of this class of targets.[10]

From the retrosynthetic perspective, the open chain form of daunosamine (**1b**, Scheme 2) could be produced by

Scheme 2



Wacker oxidation[11] at the terminus of the corresponding allylic amine. The feasibility of this approach rested on a few isolated examples of reversed regioselectivity in Wacker oxidations, observed in the presence of C−O or C−N bonds at the allylic position.[12,13] The requisite terminal alkene for this Wacker oxidation tactic could arise through silicon-tethered vinyl addition to a chiral 2,3-dihydroxyhydrazone.[3] This in turn would be conveniently available from crotonaldehyde via Sharpless asymmetric dihydroxylation.[14]

The synthesis began with the condensation of *trans*-crotonaldehyde with dibenzylhydrazine (Scheme 3). Sharpless asymmetric dihydroxylation of the resulting (*E*)-α,*β*-unsaturated hydrazone **2** afforded the *syn*-diol **3** (70% yield, 89% ee by HPLC). Silylation with chlorodimethylvinylsilane then provided the radical cyclization precursor **4** in 98% yield.

In the key step, exposure to thiyl radicals generated from PhSH and azo-bisisobutyronitrile (AIBN) led to radical cyclization of dibenzylhydrazone **4a**. The unstable cyclic intermediate was then directly treated with fluoride to afford vinyl adduct **5a** in 77% yield (dr 91:9).[15] Configurational assignment of the indicated *syn*,*anti*-stereotriad of **5a** was based on analogy with the strong precedents and was ultimately confirmed through synthesis of a daunosamine derivative (vide infra). The yield in this transformation improves on an earlier result with the corresponding diphenylhydrazone (63%, dr 88:12).[16] It is also notable that the

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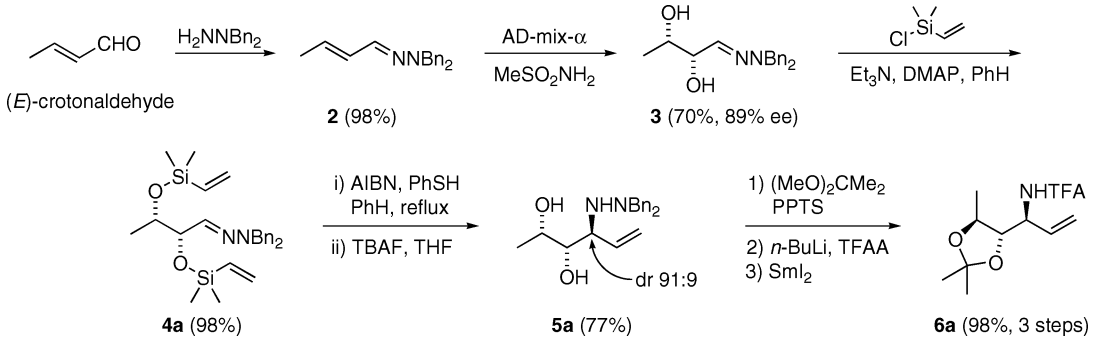
(14) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(15) The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. The inseparable mixture was carried through subsequent steps, after which the minor diastereomer was no longer detected.

(16) The earlier result was complicated by the presence of syn−anti diastereomers in the diol precursor. See ref 3. Subsequent experiments with diastereomerically pure diphenylhydrazone resulted in similar yield (65%) and improved selectivity (dr > 98:2).

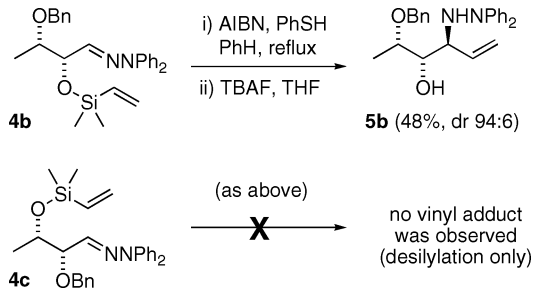
Scheme 3



dibenzylhydrazones are more stable during handling and storage, presumably due to greater resistance to air oxidation.

The silicon-tethered vinyl group was attached to both hydroxyls of the 2,3-dihydroxyhydrazone, leaving an ambiguity in the mechanism: Which vinyl group was transferred? We previously offered indirect evidence that the vinyl additions involving such 2,3-bis(silyloxy)hydrazones likely proceed through a 5-exo cyclization.[3b] We have now tested this proposition by submitting the two regioisomeric monobenzyl ether derivatives **4b** and **4c** to the vinyl addition conditions (Scheme 4). Tethering the vinyl group to the

Scheme 4



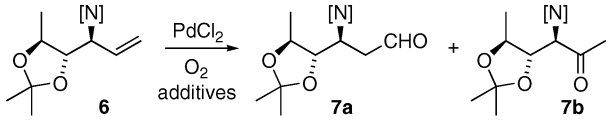
α-hydroxyl led to modest yield (unoptimized) and excellent stereoselectivity, consistent with the cyclization of the bissilyl ether. In contrast, the β-tethered substrate **4c** failed to cyclize, forming the desilylated hydroxyhydrazone as the only product after treatment with fluoride. This offers strong evidence that the vinyl transfer in **4a** involves the silicon tether to the α-hydroxyl group through preferential 5-exo cyclization.

The next challenge for the synthesis was regioselective oxidation of the terminal olefin to the aldehyde. Aldehydes are generally undesired byproducts in Wacker oxidation, a reaction commonly applied for reliable access to methyl ketones. However, as noted above, this unconventional regioselectivity in the Wacker oxidation has occasionally been observed in the presence of polar functionality at the allylic position.[12] With vinyl adduct **5a** exhibiting just such a characteristic, it became of interest to explore Wacker conditions for optimal aldehyde selectivity.

Three substrates, **6a**−**c**, with different N-substituents were prepared efficiently through a three-step protocol leading to the corresponding trifluoroacetamide **6a** in 98% overall yield (Scheme 3).

Attempted Wacker oxidations (Table 1) with the intermediates in the pathway from **5a** to **6a**, either allylic

Table 1.



substrate [N]	additives	yield, %[a]	ratio **a**/**b**[b]
—NHTFA (**6a**)	$Cu(OAc)_2$	83 (45)	54:46
—$NHNBn_2$ (**6b**)		0%[c]	--
TFA (**6c**) —N—NBn_2		0%[c]	--
6a	$CuCl_2$	80 (52)	65:35
6a	CuCl	85 (64)	75:25
6a	CuCl, HMPA	--[d] (64)	82:18[e]

[a] Combined yield of **7a** + **7b**. Yields in parentheses are for the isolated yield of **7a**. [b]Ratio (w/w) of isolated products. [c]Decomposition. [d]**7b** not isolated. [e]Ratio by ^{1}H NMR.

hydrazine **6b** or hydrazide **6c**, resulted in complete degradation. After N−N bond cleavage[17] to allylic trifluoroacetamide **6a**, however, the Wacker oxidation furnished aldehyde **7a** and ketone **7b** in yields over 80%. Although the reaction did indeed favor the desired aldehyde, the ratio (54:46) was unsatisfactory.

The effects of various copper salts were examined (Table 1). Replacing the $Cu(OAc)_2$ with $CuCl_2$ enhanced the aldehyde preference, and even better results were obtained with CuCl (64% isolated yield of aldehyde). The highest ratio (82:18) was obtained in the presence of HMPA,[12a] although the isolated yield of the aldehyde was not improved. Attempts to increase the selectivity by addition of a lithium salt led to the loss of the acetonide.

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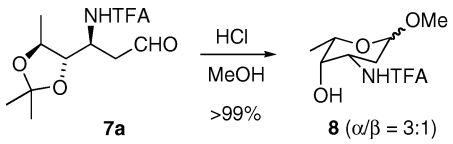
With a synthetically useful yield of aldehyde available, the synthesis of protected L-daunosamine was easily completed upon exposure of **7a** to methanolic HCl (eq 2). This



7a **8** (α/β = 3:1) (2)

resulted in removal of the acetonide protecting group and cyclization to **8**,[18] the methyl pyranoside form of the TFA-protected L-daunosamine, in quantitative yield, as a 3:1 mixture of anomers.[19]

In summary, the application of silicon-tethered vinyl addition under tin-free thiyl radical conditions was linked with asymmetric dihydroxylation and a regio-reversed Wacker oxidation to accomplish the synthesis of an L-daunosamine derivative in 32% overall yield from achiral precursors.[20]

Acknowledgment. We thank NSF (CHE-009683) for generously supporting this work, and we appreciate kind assistance to T.J. by Professor Martin Kuehne (University of Vermont).

Supporting Information Available: Preparative details and characterization data for **2**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) In another run, after prolonged exposure to TsOH/MeOH over 5 days, the α-anomer was found to predominate. Anomeric equilibration of *β*-**8** to α-**8** has been previously reported. See ref 18c.

(20) (a) Prior to this work, asymmetric catalytic routes to daunosamine derivatives had been achieved in 8−10% overall yield. Xu, Z.; Johannes, C. W.; La, D. S.; Hofilena, G. E.; Hoveyda, A. H. *Tetrahedron* **1997**, *53*, 16377−16390. Dai, L.; Lou, B.; Zhang, Y. *J. Am. Chem. Soc.* **1988**, *110*, 5195−5196. Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *J. Org. Chem.* **1983**, *48*, 910−912. (b) Other efficient syntheses of daunosamine and its derivatives from commercially available achiral or non-carbohydrate precursors range from five to nine steps and from 7−34% overall yield. For details, see Supporting Information.